114. (New) A pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of claim 92.

REMARKS

Claims 92-114 have been added to this application and claims 48-91 have been cancelled from this application without prejudice in this Reply. The application Abstract and the priority claim have also been amended in this Reply. No new matter has been added to the application by way of these amendments.

The Examiner specification and claim objections and rejections are overcome or are traversed as set forth below.

Rejection Of Claims 50-57, 60-61, 63-65, 67-71, 73-75, 79-83, 85, 87-88, and 90 over Meijer under 35 U.S.C. §103(a)

The Examiner has rejected claims 50-57, 60-61, 63-65, 67-71, 73-75, 79-83, 85, 87-88, and 90 over U.S. Patent No. 6,316,456 to Meijer under 35 U.S.C. 103(a). Applicants respectfully traverse the rejection.

The publication date of the PCT application from which U.S. Patent No. 6,316,456 is derived is shown on the face of the document as June 12, 1997, which is after the filing date of the parent of the present application (US 5,866,702, filed August 2, 1996). Thus if U.S. Patent No. 6,316,456 is available as prior art at all in the U.S., it would only be with respect to material added to the present application that is not within the scope of the parent.

The disclosure of Meijer is all within the scope of the parent application. Thus, the rejection of claims 50-57, 60-61, 63-65, 67-71, 73-75, 79-83, 85, 87-88, and 90 over U.S. Patent No. 6,316,456 to Meijer under 35 U.S.C. 103(a) is not correct, and should be withdrawn.

Rejection Of Claims 50-57, 60-61, 63-65, 67-71, 73-75, 79-83, 85, 87-88, and 90 over Schow under 35 U.S.C. §103(a)

The Examiner has rejected claims 50-57, 60-61, 63-65, 67-71, 73-75, 79-83, 85, 87-88, and 90 over Schow under 35 U.S.C. 103(a). Applicants respectfully traverse the rejection.

The same reasoning as set forth above with respect to the rejection over Meijer applies to the rejection over Schow. Schow was published in 1997, well after the filing date of the parent of the present application (US 5,866,702, filed August 2, 1996). Thus if the disclosure of Schow is available as prior art at all in the U.S., it would only be with respect to material added to the present application that is not within the scope of the parent.

The disclosure of Schow is all within the scope of the parent application. Thus, the rejection of claims 50-57, 60-61, 63-65, 67-71, 73-75, 79-83, 85, 87-88, and 90 over U.S. Patent No. 6,316,456 to Meijer under 35 U.S.C. 103(a) is not correct, and should be withdrawn.

Double Patenting

Claims 50-88 and 90 are provisionally rejected for obviousness-type double patenting as being unpatentable over claims 48-74 and 76 of copending patent application

09/929,771. When an indication is received of allowability of the present claims, Applicants will provide an appropriately drafted Terminal Disclaimer.

Rejection of Claim 91 under 35 U.S.C. §101

The Examiner has rejected claim 91 under 35 U.S.C. 101. As the subject matter of claim 91 has been canceled, this rejection is now moot. Applicants reserve the right to pursue such claims in a continuing application.

Rejections under 35 U.S.C. §112, First Paragraph

1) The Examiner states that the provisos lack description, citing Ex Part Grasselli (231 USPQ 393) for the proposition that a negative limitation requires description in the specification. Applications respectfully traverse the rejection.

The provisos are simply present to eliminate compounds that may be within the prior art from the scope of the claims (for example, the known compound olomoucine). The issue is not that there is any uncertainty introduced by such provisos -the species removed from the claims by proviso are clearly useful for their stated utility. The Board stated, relative to the issue in Grasselli:

> It might be added that that the express exclusion of certain elements implies the permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations do, in fact, introduce new concepts. Id. 399.

Equally clearly, this is not the situation in the present application. There are no "new concepts" introduced by the three provisos - they do not imply the inclusion of any other "elements".

The Examiner's rejection can be overcome by removing the provisos from claim 1. If this were done, then the result of their removal could be a first Office action rejecting the claim under 35 U.S.C. 102. Such a rejection could be then be overcome by excluding such compounds from claim 1 by proviso. Presumably the Examiner is not suggesting that Applicants have no right to do so in response to such a rejection? But the result is exactly the same as including the provisos in the instant claims.

Applicants respectfully submit that the rejection under 35 U.S.C. 112, First Paragraph, should be withdrawn.

2). The Examiner also stated that "The compounds are disclosed to be CDK-2 inhibitors. There is no reason to think that one of ordinary skill in the art could, without undue experimentation, treat such difficult disorders with such compounds". Applicants respectfully traverse the rejection.

The quantity of experimentation needed to make or use the invention is related to the content of the disclosure and to what is known in the relevant art.

> A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation. It is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification.

Northern Telecom, Inc.. v. Datapoint Corp., 15 U.S.P.Q. 1321, 1329 (Fed. Cir. 1990) (see also In re Gay, 135 USPQ at 316, Atlas Powder Co. v. E.I. Du Pont De Nemours and Co., 224 USPQ 409 (Fed. Cir. 1984).

Applicants believe that a person skilled in the art would not need undue experimentation to either prepare or use the claimed compounds. They would understand that CDK-2 inhibitors are useful in the disease states claimed, based upon knowledge freely available in the art. For example, as mentioned above, there are many issued patents that claim

novel CDK-2 inhibitors and disclose that they are useful for the utilities claimed in the instant application - see, for example, U.S. Patent Nos. 6,498,163 and 6,503,914.

The Examiner points to several articles (Glaub, Vesely, etc.) for the proposition that references of record do not support the concept that CDK-2 inhibitors are useful for the claimed disease states. Even supposing that this were true (which it is not), the articles cited by the Examiner are from 1994 and 1995 - much progress has been made in this area since then, as evidenced by Applicants invention, and the inventions of numerous patent holders.

The Examiner also states that Applicants' compounds are shown to be (in some instances) less active than olomoucine, and that, as olomoucine is not potent enough to be effective, therefore the compounds of Applicants' invention are not effective. Applicants submit that this statement is incorrect as a matter of scientific fact and of patent law.

1) Olomoucine has not been shown to be ineffective. In an abstract of a review entitled "Synthetic Cyclin Dependent Kinase Inhibitors: New Generation of Potent Anti-cancer Drugs" a reference to olomoucine states that "its unique mechanism of action and potent anticancer activity under both in-vitro and in-vivo conditions provide a unique tool to inhibit tumor cell proliferation, and to selectively induce aptosis in neoplastic tissues". (Abstracted from Advances in Experimental Medicine and Biology (1999), 457).

If the Examiner means to say that olomoucine has not been approved as a marketable product, that is correct. However, such a statement is not synonymous with the proposition that olomoucine is ineffective for its stated purpose.

2) Even if olomoucine was ineffective, the fact that some of the compounds of Applicants' invention show less activity in-vitro than olomoucine is irrelevant. Applicants clearly demonstrate that the compounds of the invention are CDK-2 inhibitors, and CDK-2 inhibitors are well known to possess the claimed utilities. As the court said with respect to research involving prostaglandins:

> Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of §112 would delay disclosure and frustrate, rather than further, the interests of the public.

In re Bundy, 209 USPQ 48, 51 (CCPA 1981)

The compounds of the present invention are novel compounds that possess significant therapeutic utility. There is no requirement that Applicants delay filing a patent application in order to carry out testing of the compound.

Additionally,

> As we said in Fouche, there is no requirement in §112 that all of the claimed compounds have the same degree of utility. Some antihypertensive activity coupled with knowledge as to the employment of this activity is all that is necessary to satisfy the how-to-use requirement.

In re Gardner, 177 USPQ 396, (CCPA 1973)

> While specific methods of use.....for each and every species covered by the claims have not been demonstrated as pointed out by the examiner, a disclosure of that extent is not required by statute. As stated by the court in In re Grimme et al., 57 CCPA 785, 274 F.2d 949, 1960 C.D. 123, 754 O.G. 6, 124 USPQ 499, 502:
>
> > "It is manifestly impractible for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every

> such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it"

Ex parte Schundehutte and Trautner, 184 USPQ 697, 699 (POBA 1974)

Applicants respectfully submit that the present disclosure is sufficient to teach those skilled in the art what the invention is, and how to use it. The rejection should be withdrawn.

Rejection Of Claims 83 and 85 under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 83 and 85 under 35 USC §112 because the compounds are not capable of treating cancer generally.

As discussed in detail previously, all of the disease states listed are known in the art to be treatable by a CDK-2 inhibitor. Such disease states are primarily cell proliferative disorders (cancer, rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis, diabetes, and graft versus host disease), or have cell proliferation as a part of the sequelae of the disease (gout, diabetes). Pathological cell proliferation may also be the result of wounding, including surgical wounding, as in the case of restenosis.

In any event, in order to expedite allowance of the claims, Applicants have amended claims 83 and 85 to include disease states that have been previously allowed in similar patents. See, for example, U.S. Patent Nos. 6,498,163 and 6,503,914, in which similar language is employed (see claim 11 of the '163 patent and claim 35 of the '914 patent). Applicants respectfully submit that one of ordinary skill in the art would understand that a CDK-2 inhibitor would have the utilities claimed in the present application.

The Examiner notes that the application discloses an additional property of the compounds of the invention as IκB-α cell cycle kinase inhibitors. Although not agreeing with the Examiner's comments, Applicants have drafted new claims that recite "A method of inhibiting a cell cycle kinase characterized as CDK2", thus rendering the rejection moot. Applicants reserve the right to pursue such claims in a continuing application.

Rejection Of Claims under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 50-88 and 91 under 35 U.S.C. §112, First Paragraph. Applicants have drafted new claims 92-114 that obviate these grounds of rejection.

Parentage

As requested by the Examiner, the statement regarding the parentage of the application has been amended.

Abstract Amendment

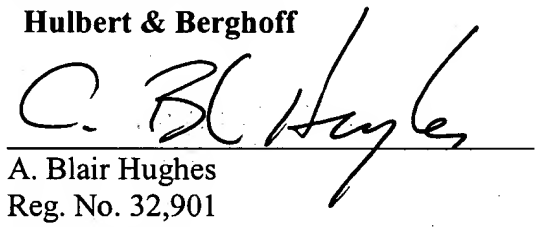
The Abstract has been changed to what is considered to be an acceptable format.

CONCLUSION

The amendments and/or statements in favor of patentability presented above are believed to render pending application claims 92-114 allowable. Favorable reconsideration and allowance of all pending application claims is, therefore, courteously solicited.

Respectfully submitted,

McDonnell Boehnen Hulbert & Berghoff

Dated: March 7, 2003 By: 

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